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Human pluripotent stem-cell-derived cardiomyocytes in cardiovascular drug discovery and development

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Abstract

Cardiovascular disease (CVD) is an alarming health problem responsible for a large percentage of fatality worldwide. Current treatment is limited and research is ongoing to address this serious health problem. As mortality rates rise, the demand for novel therapeutics has pressed the pharmaceutical industry to explore alternative approaches for CVD drug development. Human pluripotent stem cells (hPSCs) hold great promise in bringing new effective cardiovascular treatments to the market through providing an improved testing platform for pre-clinical drug screening. Both stem cells derived from pre-implantation human embryos or somatic cells by reprogramming are under intense investigation for their potentially valuable attributes of cell renewal and pluripotency. This approach aims to overcome the lack of appropriate human cardiac disease models for toxicology testing by providing a novel system that is scalable, reproducible and from an inexhaustible source. Here we review the opportunities for cardiomyocytes derived from human stem cells in the field of cardiovascular drug development.

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Cardiovascular Disease: an alarming health problem

Cardiovascular disease remains one of the main causes of morbidity and mortality worldwide, leading to more than 17.5 million deaths worldwide per annum [1]. CVD is an umbrella term for all diseases of the cardiac muscle and circulatory system, including heart failure, stroke, atrial fibrillation and cardiomyopathy. Due to the complexity and severity of certain types of CVD, patients often prove unresponsive to current medical treatments, which are limited in both availability and effectiveness.

As the disease remains one of the most prevalent medical conditions throughout the UK, the demand for new pharmaceutical drugs is soaring. Research in the realm of cardiovascular drug discovery and development is ongoing, however many challenges are yet to be overcome. The lack of appropriate cardiac disease models for toxicology testing has provoked the need for a novel system that is scalable, reproducible and from an inexhaustible source.

The drug discovery and development process is often long, complex and expensive; however innovative research in the field of medical and pharmaceutical biotechnology has led to new advances in the use of human pluripotent stem cells. This review aims to evaluate the promising opportunities that pluripotent stem cells give rise to in the new era of cardiovascular medicine.

Cardiovascular Disease: the need for change in the drug industry

The cardiovascular drug industry has been plagued, over the past decades, with a large volume of molecular targets thanks to the sequencing of the human genome

and the reliance on high-throughput screening (HTS) in order to identify and optimise drug candidates. However this reductionist approach, of one-target one-drug one-effect paradigm, is associated with numerous flaws [2]. Currently failures of drug candidates identified in initial screens leads to an estimated one-third of drugs being withdrawn from the market and the expenditure lost as a consequence has left the drug development industry sore [3]. The lack of physiologically relevant preclinical models has been identified as a cause of inefficacy where preclinical trials of therapies have often looked to animal models. This offers an explanation as to why the efficacy of translating successful in vitro drug candidates into clinical trials has yielded disappointing outcomes - <10% of compounds that enter the clinical phase of testing achieve market approval, with estimated costing of $1.2-1.7 billion per drug [4]. However, the drug industry is undergoing radical change and is moving away from this so called reductionist approach and embracing new potentials [2].

Presently the reliance on immortalized cell lines - animal models of human disease and clinical trials - are consistent with the drug discovery process. This process has often been portrayed as a long, expensive and complex journey. Together with disappointing advances, the drug industry is facing increasing and growing concerns over the efficacy and safety of drug discovery. This has prompted and encouraged the drug industry to re-consider how new medicines are developed. One highly promising offering is the development of a more physiologically relevant in vitro model, which harbours the potential for enhancing the likelihood for successful translation of preclinical discoveries into clinical treatment. By using an improved testing platform the incorporation of the complexity of the clinical human disease phenotype can be achieved, addressing and potentially overcoming the limitations of current testing platforms [5].

Drug discovery and toxicology: seeking a reliable test system

It would be immensely valuable if a reliable test system, which would allow for the identification and characterisation of potential drug targets; the screening of compound libraries for the selection of drugs with desired effects; the detection of drug candidates; and the identification of potential associated adverse effects, could be developed for CVD [6-9].

The limited regenerative capability of human cardiac tissue, and difficulties in both obtaining and propagating cardiomyocyte cells out with the human body for drug testing, has provoked the need for new methodological developments for cultivating cardiomyocytes in vitro. Currently, studies investigating novel therapeutics for CVD involve the use of animal models. There are, however, both scientific and ethical problems associated with their use. In addition, primary myocytes derived from animal models, including rodents, have been used as models of cardiac response. However, as with human cardiac cells, they are limited in their ability to survive in culture media out with the body. The use of animal models in drug testing is also limited due to the physiological differences between animals and man. For instance, when drugs are administered orally, the main site for absorption is the small intestine. The half-time for stomach emptying in rodents is approximately 10 minutes, whilst in comparison humans have an estimated stomach emptying half-time of 1-2 hours. This is considerably longer and therefore drug absorption is significantly quicker in animals compared to humans [10]. There are also notable differences in metabolism within the liver between humans and animals. Drug compounds are eliminated by the liver and excreted via the urine and bile at a quicker rate in animals. Experimental animals have relatively greater body surface area to body weight ratios compared to humans. As a consequence, the rate of metabolism to maintain internal homeostasis is greater in animals, than humans. Biological characteristics, including lung volume, respiratory rate, kidney/liver size and heart rate all vary dramatically between species, and should be considered when comparing animal responses to predicted human response in drug testing [11]. Finally, as there is a notable difference in hepatic metabolism between species, drug dosage concentrations affect animals differently to humans. This is due to increased toxin elimination as a result of the 'first-pass effect' in animals, whereby a portion of the drug is eliminated during passage through the liver before entering the circulatory system. Although the involvement of animal models has long been associated with biomedical research such interspecies differences create difficulties in translating and interpreting some diseases in animal models into credible clinically significant findings in human disease. Thereby, it is essential that interspecies differences are considered and controlled, if possible, during the pharmacokinetic pre-clinical drug testing stage [11].

Over the years, concerns have been increasingly expressed regarding the progression attrition of pharmaceutical products in the long pipeline between "hit" identification and the market [4]. Many of these concerns are directed at the use of animal models which are consistent with a majority of toxicity screens. A lot of doubt has been cast on the safety of such testing through questioning the assays translatability to humans. The involvement of animal models is deemed an essential step in drug development for determining in vivo efficacy and toxicological properties of prodrugs [3]. However it

is hard to ignore the marked differences in physiology between humans and animals. This has contributed greatly to the significant lack of conformity between current testing procedures and human outcomes, especially in the evaluation of toxicity and drug dosing [5]. Alarmingly a survey of pharmaceutical companies displayed that data obtained from rodents failed to predict 60% of human toxicity incidents held accountable for 30% of drug failures in clinical trials. The severity of such failures was highlighted by the tragedy of the "elephant man" trial at a London hospital in 2006 [3]. This greatly emphasises the need to design a human based toxicity assay for a more efficient means of detecting toxicity. One promising avenue is the use of human stem cells, which potentially harbour great expectations in overcoming the issues currently associated with pharmaceutical toxicity testing.

Stem-cell-derived cardiomyocytes: paving the way to safer and more effective cardiovascular medicines

The intriguing and exciting prospects for stem cells with properties of self-renewal, clonogeneticity, and multi-potentiality, have been hailed for many years to offer enormous potential in the study of disease and have generated great expectations in relation to possible applications [6, 12-14]. Innovative research in the field of medical and pharmaceutical biotechnology has led to the ability to derive both human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) by differentiating embryonic blastocysts and reprogramming adult fibroblasts, respectively. Human pluripotent stem cells hold great promise in both research and medicine due to their unique ability to self-renew and their developmental potential to form various cell lineages in the body; capable of differentiating into many specialized cell types required for research – including cardiomyocytes, hepatocytes, neurons and muscle cells. The ability to differentiate stem cells into human cardiomyocyte cells with cardiac-specific characteristics, including structural, functional and molecular properties, has led to unique opportunities in the realm of cardiovascular research.

As both hESCs and hiPSCs originate from a human source, they provide a more reliable representation of human cardiovascular tissue compared to animal tissue, offering physiological relevant expression, metabolism and responses. Stem cell technology also allows the propagation of cardiomyocytes to a high quantity, providing a readily available source of human cardiomyocytes opening new doors for the study of cardiovascular disease. The limited cell derivation and cell number in cardiac tissue has often caused difficulties in the study of cardiovascular disease in existing cardiac cell models. Moreover, with access to differentiated cardiomyocytes from patients with various cardiovascular diseases or healthy human cells engineered to consist of disease specific genetics, paves the way for greater predictive accuracy in pharmaceutical research, pre-clinical studies and toxicity assessment.

A well-known, however not yet resolved issue is the warranted safety of novel drug compounds within the drug industry. However, the development of a toxicity screen with human pluripotent stem cells offers a promising solution in providing a far greater indication of a drug's potential toxicity than conventional animal models. The fear of replicating drugs such as thalidomide, tested with no effect on prenatal development on rodents but presenting lasting devastating defects on the development of several children [9], has haunted the drug industry. A transition away from the sole reliance of toxicity screening on animal models is therefore much desired. The reduced use of animals in toxicity screening will work two-fold: it will allay public concerns over animal testing; and more importantly address the issue of animal models as poor indicators of drug efficacy [15].

The potential of human embryonic stem-cell-derived (hESC) cardiomyocytes

The revolutionary identification of mouse embryonic stem cells (mESC) by Professor Martin Evans in 1981 initiated the development of stem cell research and lead to the identification of human embryonic stem cells (hESCs) [16]. Although murine models are currently used in stem cell research with the intension of translating data into the field of human biomedical science, investigations have identified definite differences between mESC and hESC lines. These include variations in pharmacology and nuclear transactions (e.g. DNA repair), and consequently, differences in cell fate during the differentiation process [17].

hESCs are derived from human blastocyst-stage embryos that are surplus to the requirements of in vitro fertilisation and have the capacity to self-renew indefinitely and provide a readily available source of all cell types of the human body as they have the ability to differentiate into all three embryonic germ layers, including the endoderm, mesoderm and ectoderm [12]. This is a considerable benefit over the use of primary animal cell lines, and over 800 normal and genetic disease-bearing lines have been developed in research laboratories to date. hESCs can be continuously propagated within an in vitro artificial culture medium and have the capability of producing de novo cardiomyocytes which represent all phenotypes of the heart, including ventricular, atrial and nodal cells.

hESCs are most frequently used in cell replacement therapy, including bone marrow transplantation in the treatment of leukaemia. However recent advances have

demonstrated the successful application of embryonic stem cells in cardiovascular drug discovery and testing, as well as disease modelling. In order to evaluate the efficiency of a new drug at preventing or reversing a CVD process, the hESCs are firstly differentiated into a cardiomyocyte cell line (hESC-CM). The targeted disease is then induced within the cells, usually through transfection using DNA plasmids to generate transgenic cells. This creates a model, which is similar to that of a transgenic animal; however through the use of hESC-CMs the ethical considerations that accompany the use of animals are avoided (Figure 1).

iPSCs – transforming the outlook of cardiovascular diseases

In 2007, the discovery of induced pluripotent stem cell (iPSC) technology was considered a milestone in regenerative medicine and offered a novel opportunity to model cardiovascular disease and evaluate new therapeutics. Since the concept of iPSC technology was first explored, approximately seventy hiPSC models of rare and complex human diseases have been published and current momentum is further increasing this [5]. The appeal of reprogramming somatic cells to a pluripotent state with the ability to differentiate into any cell type found within the human body was greeted with enormous optimism. Rewarding benefits were foreseen, especially for cardiovascular medicine where cardiomyocytes from human probands or patients are extremely difficult to obtain. With iPSC technology affording a way to an unlimited source of patients' pluripotent stem cells, through a non-invasive isolation technique and simple genetic manipulation using transcriptional factors, a potentially valuable attribute in drug development and drug toxicity was revealed. Drug development/discovery platforms involving iPSC-based phenotypic disease assays bear the potential to fulfil the gap observed between animal models and clinical trials [6] by offering greater versatility and improved relevance in modelling cardiovascular disease.

iPSC technology has unprecedented potential to reconfigure genetically identical tissues whether healthy or in a disease state to screen possible therapeutic compounds to determine efficacy in particular diseases. The scope for modelling disease using iPSCs is greatly diverse. iPSCs differential capacity to become all cell types of the body serves as a potentially unlimited ex vivo source of human derivatives. The genetic diversity offers a magnitude of distinct disease phenotypes, some of which may not be possible in animal models. This will facilitate a powerful insight into mechanisms behind an array of diseases allowing for the effective study in the view of developing diagnostic or therapeutic applications [5].

Current applications of human pluripotent stem cells in drug screening

Studies into the effects of various compounds for preventing and reversing CVD in cardiomyocytes, derived from hESCs, is currently ongoing. The research involves the differentiation of stem cells into individual

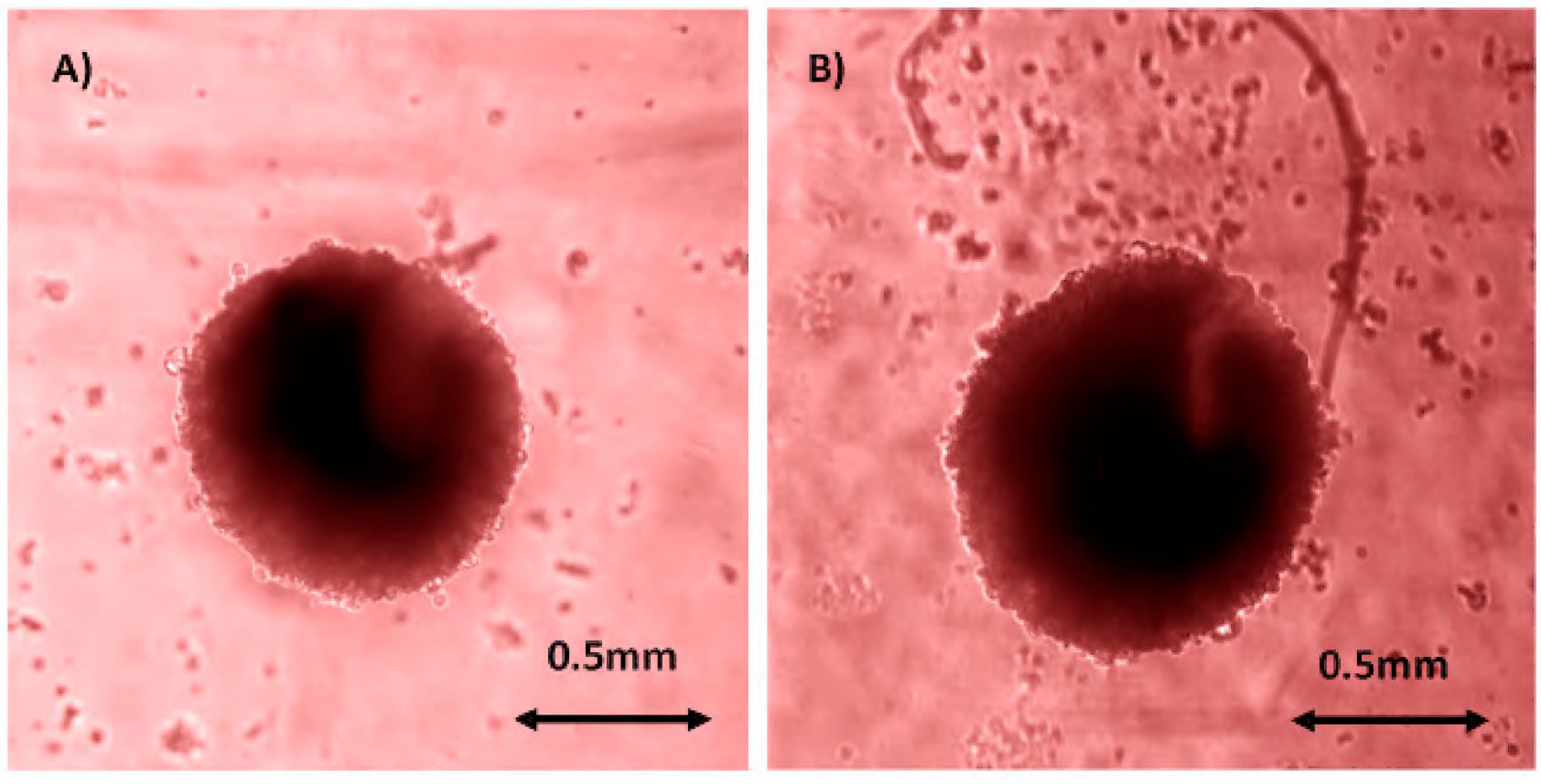

Figure 1. Cardiomyocytes derived from hESCs as a model of cardiac hypertrophy. A) displays a 'mini-heart' consisting of a population of healthy cardiomyocytes. In contrast B) demonstrates the successful in vitro induction of a hypertrophic stimulus to achieve a human cardiac hypertrophy phenotype. The diseased state was induced using human angiotensin II, significantly increasing the cellular mass of the cardiomyocyte cells. Pictures provided by autors.

mini-hearts, composed of cardiomyocyte cells. This has provided grounding for cardiovascular drug discovery and development testing to be carried out [19]. The mini-hearts contract regularly, and similarly, to normal human cardiac muscle and can be treated with various drug compounds. Ongoing research carried out at Abertay University in Dundee, has attempted to discover a curative treatment for Hypertrophic Cardiomyopathy (HCM). HCM is an autosomal dominant condition of the cardiomyocytes whereby the ventricles of the heart muscle become thickened and enlarged (hypertrophied). The disease is estimated to affect 1 in 500 individuals in the UK, and has been identified as the most prevalent inherited cardiovascular disorder worldwide [20]. The sporadic, non-familial, form of the disorder is the leading cause of sudden cardiac arrest in young athletes. As of yet, no effective therapeutic treatment has been established for its treatment; however various studies have made attempts at resolving this medical issue.

Previous research has identified the involvement of the CDK9-related kinase pathway as a key factor in the induction of cardiomyocyte hypertrophic growth (Figure 2). The study suggests that the positive transcription elongation factor b (P-TEFb), which consists of several regulatory subunits, including CDK9, is involved in the disease process when a 'normal' healthy heart becomes hypertrophied. The catalytic CDK9 component of the P-TEFb subunit was found to play a key role in the hyper-phosphorylation of the enzyme RNA polymerase II (pol II), in response to hypertrophic stimuli, and trigger transcriptional elongation and ultimately lead to hypertrophy. It has therefore been suggested that cardiac hypertrophy can be blocked through the use of small CDK9 inhibiting molecules [21].

Research into the effectiveness of CDK9 inhibiting compounds as pharmaceutical drugs for targeting P-TEFb-dependent cardiac hypertrophy, has previously been performed using murine models [23]. The results are positive, although due to significant interspecies differences between the physiology of mice and humans, CDK9 inhibition could not be proven as a target in human patients. It is therefore essential that the effectiveness of CDK9 inhibiting drugs is performed on human cells. However, as human cardiac cells do not have the capacity to regenerate, and are difficult to both obtain and propagate in vitro, human stem cells (hESCs) have been suggested

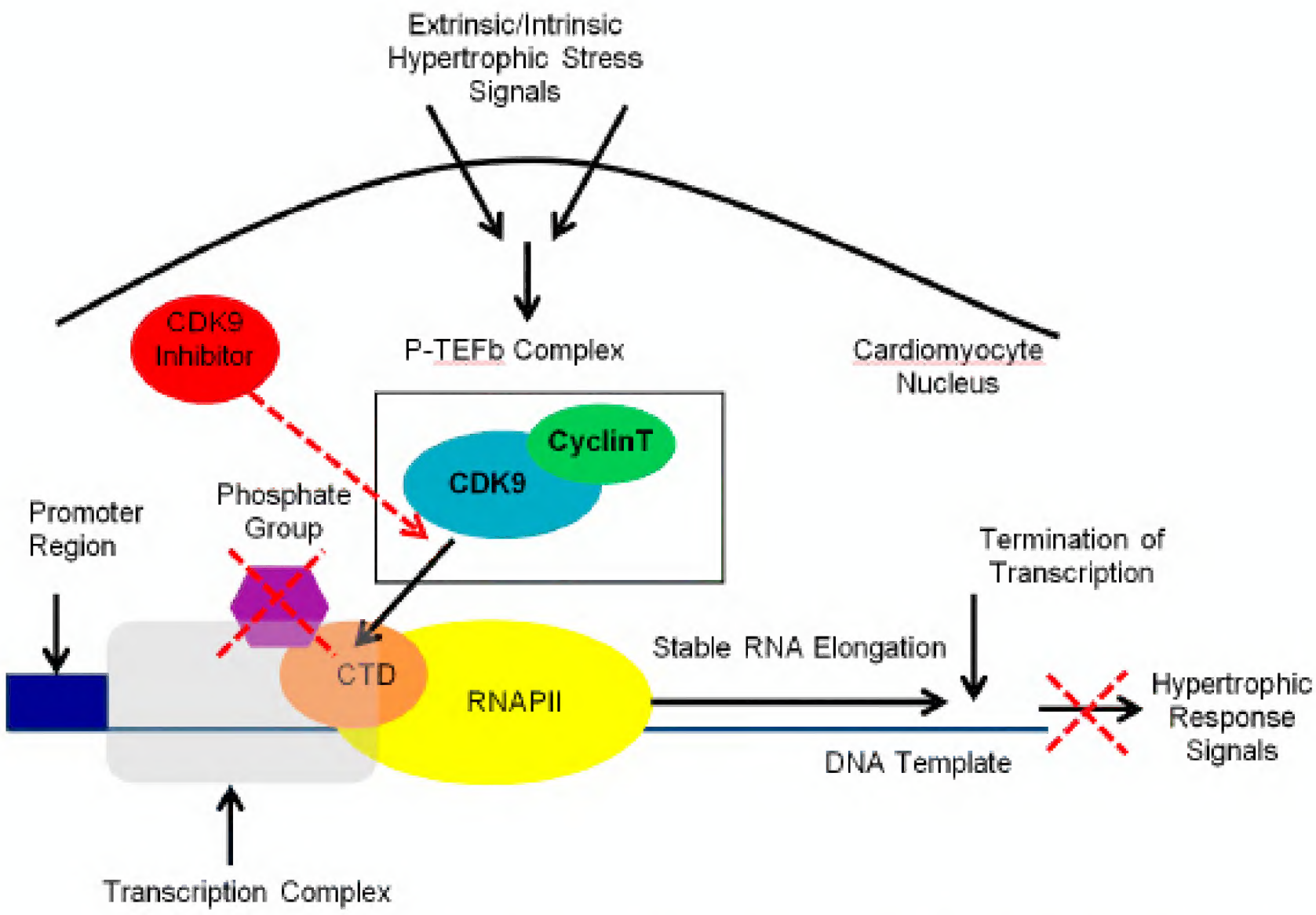

Figure 2. Phosphorylation of the carboxyl-terminus (CTD) domain of RNA pol II via the catalytic CDK9 subunit of the P-TEFb complex. Figure 2 displays the role of CDK9 in stabilising transcriptional RNA elongation. In response to hypertrophic stress stimuli, the CDK9 subunit (blue) binds to the CTD domain (orange) of RNA pol II (yellow) causing phosphorylation and RNA elongation, and ultimately leads to a hypertrophic response. The hypertrophic response signal leads to changes in the physiology of the cardiomyocytes. However, the pathway can potentially be blocked through the introduction of a CDK9 inhibitor (red), which binds to the CDK9 subunit preventing it from binding to the CTD domain. This blocks both the phosphorylation of RNA pol II and elongation of RNA, and prevents hypertrophic response signals from causing physiological changes in the cardiomyocytes cells [22].

as a means of overcoming these issues.

The use of Roscovitine, a drug known to inhibit CDK-related activity in tumour cells, has demonstrated positive results in the prevention of cardiac hypertrophy [24-27]. The results suggest that cardiac hypertrophy is accompanied by activation of CDK9, and that target based inhibitors of the kinase pathway may be suitable molecular targets for therapeutic intervention in HCM. During drug discovery testing of Roscovitine, drug stability of the compound in media using high performance liquid chromatography (HPLC) was performed as a preliminary test. Various concentrations of the compound were used to dose hypertrophic mini-hearts, derived from hESCs. The effectiveness of the compound at preventing and reversing HCM could then be evaluated through analysing microscopic measurements of the size (volume) of the cardiomyocytes. Bioavailability analysis, as well as cytotoxicity testing has also been undertaken to investigate whether the compound has any toxic effects on 'healthy' cardiomyocytes. The results of the drug discovery investigations were positive; therefore Roscovitine is undergoing further phase II pre-clinical safety studies before the commencement of patient clinical trials, if successful.

Furthermore, new stem cell technologies such as in vitro-differentiated human pluripotent stem cell (IVD hPSC)-derived mini organs, have the potential to transform the drug discovery process [3]. An array of recent studies has supplemented this statement. This includes Liang et al. 2013 [28], who presented a collection of hiPSC-derived cardiomyocytes from patients with hereditary cardiac disorders and demonstrated the replication of drug induced cardiotoxicities and the detection of differing susceptibility among patient-derived cells. Studies such as this fundamentally outline a paradigm in which patient biology and physiologically relevant assays in human cells could help carve the route to safer and improved efficacious medicines in drug discovery.

The array of human disease modelled using hiPSCs is forever growing with a current differentiation repertoire of over 200 types of somatic cells [4]. Phenotypic assays are reliant on the expression of a physiological endpoint in contrast to interrogation of a sole target. This gives the means for developing drugs against complex diseases whereby patient-specific iPSCs allow for both genetic information and phenotypical attributes of human disease to be analysed. This opens potentially renewed and insightful knowledge on the pathophysiology of both familial and sporadic human diseases. Furthermore, as hiPSCs can represent the characteristics of the donor's clinical phenotype, this may prove especially insightful for studying diseases associated with incomplete penetrance [5] whereby cellular characteristics, which may not be clinically evident in the patient, can be uncovered.

Numerous proof-of-principle examples of late have been reported of IVD hPSC-cells from patients with monogenic disorders or engineered disease gene mutations recapitulating disease phenotypes in vitro [2]. The first studies aimed at modelling cardiac diseases using this approach were monogenic channelopathies, including different subtypes of long QT syndrome or cathecholaminergic polymorphic ventricular tachycardia (CPVT). In initial studies, drugs of known effect were used to demonstrate that in vitro disease models could recapitulate the dominant features of the disease. Now having evidenced and gained confidence in the workings of this developing technology, some studies are testing novel pharmacological concepts. For instance dantrolene, known to be administered in the clinical treatment of malignant hyperthermia, has been reported to revert the arrhythmogenic phenotype in cardiomyocytes [29] and a novel RNA-based treatment strategy has recently been investigated for long QT-syndrome [30].

Obstacles in the face of stem cell technology

One of the greatest obstacles to overcome when using hESCs in drug discovery and development is the control of differentiation. As embryonic stem cells are undifferentiated, it is often difficult to control the exact differentiation of the cells. This means that, due to chromosomal abnormalities, the cells could potentially become tumorous if they begin to grow and divide uncontrollably. It has been suggested that hESCs should be molecular cytogenetically characterised in an attempt to understand tumour initiation and progression. [31]. Likewise, incomplete reprogramming of hiPSCs from somatic cells is an additional hurdle. The idea of incomplete reprogramming to a pluripotent state arose from comparison studies between hiPSCs and hESCs. In addition to the differences witnessed between hiPSCs and hESCs reprogramming differences were also evident between clones of hiPSCs. This has offered an answer for the variation observed in hiPSC lines, which is problematic especially when scaling up hiPSC disease models for in vitro testing as this variability will influence the reproducibility of the results. Also the reprogramming of somatic cells to a pluripotent state often introduces genomic instability [5]. Consequently, incomplete reprogramming and interline variability represent a notable issue in translating from hiPSC in vitro to clinical trials and is a considerable hurdle that must be overcome to prevent deterring the utility or stalling the progress of iPSCs technology.

Limitations of hESCs lies with the high expense associated with propagating and maintaining the cells, as well as the extensive time required to successfully

differentiate/mature the stem cells into cardiomyocytes. Many have also doubted the suitability of iPSCs technology in drug development simply due to time constraints as the production of the desired cell type can be a protracted process which conflicts with the fast moving drug development industry. Moreover iPSC technology also faces legal obstacles - complexity in designing appropriate consent forms for the use of immortalised cell lines [2].

Through time, hESCs may develop uncontrollable karyotypic changes that result in physiological changes. Ultimately, the cells may undergo genetic selection and adaption to the in vitro culture media environment. hiPSCs have an extremely low efficacy to harvest, and are therefore increasingly expensive to reprogramme, cultivate and maintain compared to hESCs and animal cell lines. Another line of thought is that the phenotypes expressed by hiPSCs-derived cells are developmentally immature compared to their in vivo-derived counterparts and may not exhibit full functionality [15]. Uncertainty therefore remains over the ability of hiPSCs-derived cells to reach the necessary endpoint to truly evaluate the phenotype or pathways of interest.

As hiPSCs originate, and are reprogrammed, from somatic cells that are already differentiated, any existing genetic mutations within the patient's genome will be passed through the hiPSCs. The presence of a secondary genetic condition could potentially affect the responsiveness of the cell model to drug treatment [32].

With a large volume of protocols inevitably a large level of variance will follow in relation to repeatability and robustness in generating scalable, homogenous cell populations. In contrast the IVD protocols for numerous cell types are lacking. The lack of standardisation is an issue and one that needs to be resolved if pluripotent stem cell technology is to become an integral part of drug development [2]. Furthermore it has become increasing apparent that the anticipated pace of incorporating practical applications of hESCs and hiPSCs has fallen short because of the technical challenges and reluctance of industry leaders to embrace stem cell technology [2]. Concluding that the development of robust differentiation protocols and reliable assessments of the functionality of PSC-derived disease models are required before stem cell technology can become fully integrated into the process of drug development [5].

Looking forward

Fulfilling the potential of stem cell technology in the drug development industry necessitates the standardisation of protocols. Once achieved the possibilities and applications for stem cell technology are vast.

Using human pluripotent stem cells in cardiovascular medicine not only addresses the contentious issue of animal models but offers great scalability with the potential of high-throughput screening. The use of patient specific hiPSCs on a small scale could allow for the identification of side effects prior to the drug being administered to the patient. However, a more feasible approach for the use of hiPSCs in drug toxicity is on a large-scale due to the current expense of creating and maintaining pluripotent stem cell lines [5]. With the potential for generating continuous supplies of progenitor cells, the ease of scaling up for high-throughput testing offers a new dimension for safety testing. Additionally, the culturing of iPSCs-derived cells of various tissue types in large grids and assaying for toxicity in an analogous form will enable high-throughput screens for drug discovery. Proof-of-concept toxicity studies performed with human iPSC-derived differentiated cell types support this approach [15].

In 2008, the President's Council of Advisors on Science and Technology (PCAST) articulated the concept of "personalised medicine". Personalised or precision medicine explores the notion of designing a medicine based on a patient's genetic make-up and specific disease characteristics in the hope of increasing therapeutic benefits while reducing the risk of adverse effects [2]. iPSC technology has the potential to make this concept of personalised medicine a reality – hiPSCs can be produced via epigenetic reprogramming of adult somatic cells, allowing for a growing genetically diverse pool of patient specific cells. The development of a robust and personalised model of disease is a major attribute iPSCs technology can bring to the forefront of drug development. The opportunity to model the developmental course of a degenerative disease within each patient, modelling individual patient's disease states in vitro, personalised pharmacologic screens, individual genomic testing are all plausible through iPSC technology [33].

iPSC technology affords an opportunity to model patient-specific iPSCs derived from individuals with known susceptibilities or resistances to different drugs or diseases to assess and predict patient drug responses. This "patient in a dish" concept can expand further to uncover the niche of genetic and potential epigenetic factors that influence the variable drug responses witnessed within the population and within different subsets of patients [33]. With this knowledge, the expanding population of patient specific cells can be divided into subpopulations based on the likelihood of improved clinical outcomes and fewer side effects by accounting for genotypic differences related to disease and ethnicity. It is widely recognised that drug responses vary significantly within the population where a drug may preferentially cause adverse effects in certain individuals with particular genetic backgrounds or environmental history. Currently, patient susceptibility to

a particular therapeutic agent cannot be determined in vitro [9]. Hence, iPSC technology enables the enhancement and optimisation of the therapeutic drugs offered to patients by allowing for the selection of drugs with the greatest efficacy and with the fewest side effects [2].

The benefit to the drug industry financially, through the use of human pluripotent stem cells-derived cardiomyocytes offering a more sensitive assay for candidate drug toxicity and safety compared to previous conventional methods, is recognised. hiPSCs or hESCs screening has the potential to lessen the costly recall of already approved drugs and promote the development of a new generation of safer drugs through an alternative and less expensive strategy [34].

In addition to introducing low costs of development, human pluripotent stem cells offer the potential to increase the production of candidate compounds in a shorter turnaround time with the detection of life-threatening toxicity in a multitude of tissues. Of particular interest is the ability of iPSCs to recapitulate the process of development from embryo to adult tissue, offering a niche to test drug toxicity in developing tissues and opening a new possibility for safety testing for teratogenicity [5].

Concluding Remarks

The field of cardiovascular research is advancing rapidly and research into the development of successful therapeutic drug treatments is ongoing. The development of human pluripotent stem cells for use in the field of medical and pharmaceutical research has revolutionized the drug discovery process. By using human derived stem cells, we are now able to gain a deeper understanding of the effects of drug compounds on the human system prior to human clinical trials. Although research into the uses of stem cells in drug discovery, and more specifically cardiovascular research, is still under investigation, the high reproducibility, readily available source of cells and potential to generate into multiple cell types suggests promising outcomes for the future of stem cell research.

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